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TITLE: Synthesis and Screening of Novel Substituted Biphenyl Proteomimetics as Potential Anti-Estrogenic Agents for the Treatment of Hormone-Responsive Breast Cancer

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14. ABSTRACT The goal of this project was to identify one or more novel compounds that would inhibit estrogen receptor coactivator binding proteins. The specific aims involved preparing the requisite aryl halide and boronic acid intermediates, coupling to generate the small biphenyl library and evaluating the compounds in a competitive binding assay. Molecular modeling would be used to help design the compounds and to interpret the results. Molecular modeling suggested that the biphenyl-bis ethers would correctly occupy the target binding site. A series of acidic and basic phenoxy halides were prepared. Conversion to the subsequent aryl boronic acids was less successful and simpler analogs were prepared instead. Model Suzuki couplings were successful and coupling of the aryl halide intermediates with the available aryl boronic acids are in progress. No final compounds are in hand at this time and therefore biological results are unavailable.					
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1. Introduction

This proposal focused on the design, synthesis and preliminary evaluation of a series of biphenyl derivatives that would compete with co-activator proteins for the estrogen receptor co-activator box binding site. These compounds would be prepared using the Suzuki reaction from the requisite functionalized aryl halides and boronic acids. These intermediates also required synthesis from available starting materials. Ultimately, binding assays would indicate which substitution patterns most closely resemble the LXXLL motif found in the native protein.

2. Body

The specific aims for this Concept Award included the design of the target compounds using molecular modeling of the binding site, synthesis of the requisite aryl halides and aryl boronic acids, coupling and deprotection to yield the target biphenyl proteomimetics, and initial competitive binding assays.

A. Design of the target compounds.

The target compounds (Figure 1) were designed based on docking putative functionalized biphenyl compounds into the estrogen receptor co-activator box binding site. Preliminary molecular dynamics studies with the compounds suggested that the side chains would be accommodated within the binding pocket, although no quantitative data were generated.

B. Synthesis of intermediates and final compounds.

The synthesis of the aryl halide intermediates (Scheme 1) was achieved in good yields from the starting 2-substituted phenols. Monobromination with tetrabutylammonium tribromide gave the 4-bromo derivatives in 75-85% isolated yields. These intermediates were converted in good yields to the corresponding ethyl phenoxyacetates using the Williamson ether synthesis. The Mitsunobu reaction of the phenol with N,N-dimethylaminoethanol gave the corresponding ethers in good yields as well. Initial efforts to convert the dimethylaminoethoxyphenyl bromides to the corresponding phenyl boronic acids using the Grignard reaction did not go well, as low yields of impure materials were obtained. Alternate methods for generating the desired phenyl boronic acids for both the basic and acidic components are currently being explored.

Because of the difficulties involved with the synthesis of the requisite substituted phenyl boronic acids, model reactions were run with commercially available boronic acids that may be applicable, in some fashion, to the project. The Suzuki coupling reaction was performed with two phenyl boronic acids (Scheme 2). The coupling of phenyl boronic acid with the simple dimethylaminoethoxyphenyl bromide gave a 40% yield of the coupled biphenyl (inseparable from the starting phenyl bromide). Use of 4-hydroxyphenyl boronic acid gave a biphenyl product in slightly better yield and separable from the starting material. This indicates that the final step will succeed when we are able to prepare the requisite substituted phenyl boronic acids.

C. Competitive binding assays.

Because no final compounds in our target series were prepared, no work on this task was undertaken in the reporting period.

3. Key research accomplishments.

- Molecular modeling of putative compounds in ER-coactivator box binding site
- Synthesis of requisite substituted phenyl bromide intermediates
- Demonstration of Suzuki coupling of substituted phenyl bromide to simple phenyl boronic acids

4. Reportable outcomes

The results of this project were reported at the ERA of HOPE meeting in Philadelphia, PA on June 8-11, 2005. Poster 16-14

5. Conclusions

The project did not achieve all of the targeted milestones within the allotted timeframe. While most of the synthetic steps proceeded as anticipated, the conversion of the substituted phenyl bromides to the corresponding boronic acids was unsatisfactory using the classical Grignard methodology. Efforts to effect this conversion using alternate methods are continuing. Given the successful coupling of simple analogs of the intermediates, it appears that once the phenyl boronic acids are in hand, the final compounds should be readily prepared. Testing of those products in the competitive binding assay, which is available, will then demonstrate the feasibility of this approach to novel antiestrogenic agents.

6. References

None.

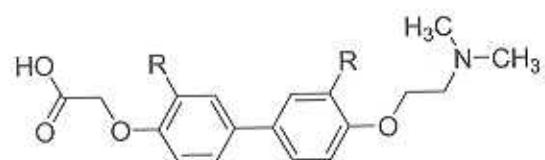
7. Appendices

Figure 1

Schemes 1 and 2

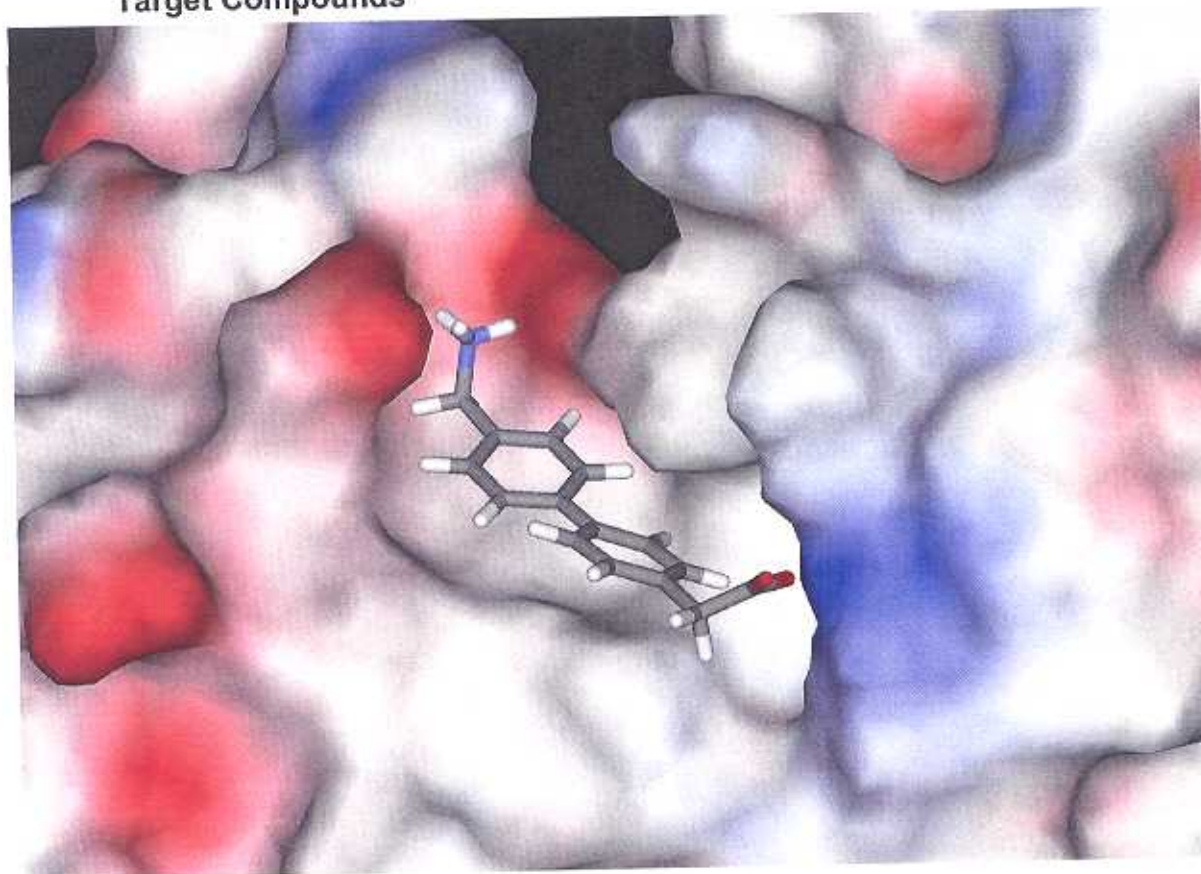
Appendix

Figure 1. Target compounds and docking of putative compound.



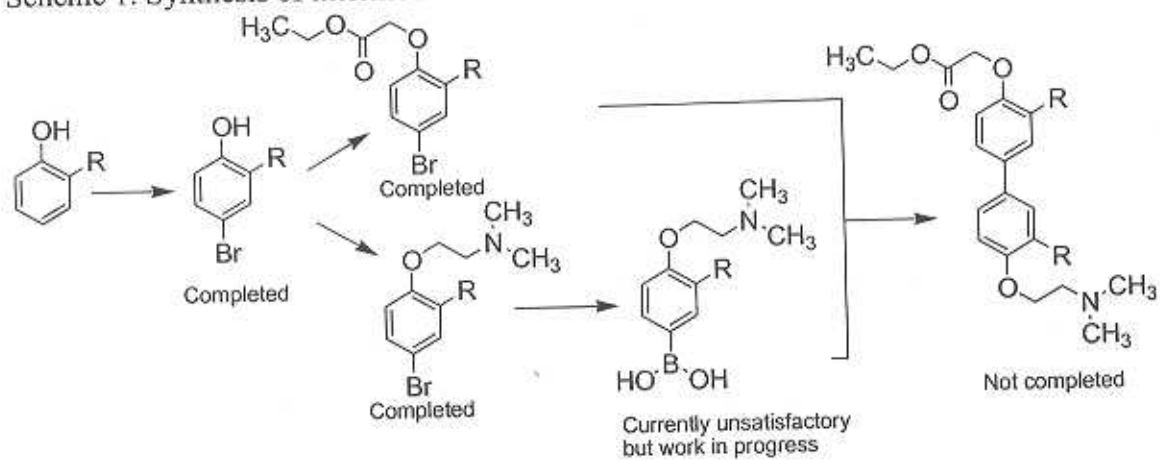
R = H, CH₃, CH(CH₃)₂, CF₃, CH₂C₆H₅

Target Compounds



Simple analog docked in ER coactivator box binding site.

Scheme 1. Synthesis of intermediates.



Scheme 2. Suzuki coupling of phenyl bromide with phenyl boronic acids.

